PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study
AUTHORS	Neovius, Martin; Jacobson, Stephan; Eriksson, Jonas; Elinder, Carl-Gustaf; Hylander, Britta

VERSION 1 - REVIEW

REVIEWER	David Goldsmith Guy's and St Thomas' Hospitals London UK
REVIEW RETURNED	10-Nov-2013

GENERAL COMMENTS	Neovius et al try to show, from a single population group in Stockholm Country over 11 years, the impact of chronic kidney disease on mortality. I think for a general journal a brief reminded of CKD stages is appropriate. The lack of any data on albuminuria, proteinuria, as powerful a driver for adverse outcomes as is GFR, needs to be clearly stated at the outset. I am assuming also that all biochemical values have been repeated in all patients to assure that this population is free from acute kidney injury cases. The real prevalence of kidney disease will be higher than the cases reported here, for this reason (above) and also the lack of data on people with normal GFR but significant urinary protein excretion. There are no data I can find on race. Certain parts of Sweden eg Malmo have very significant ethnic diversity. This is less so in Stockholm but has increased there over time. Race is a complex factor with CKD - IndoAsian and Afro-Carribean people have a much higher incidence of renal disease than Whites. Their longevity and mortality may well be different from white Swedes, who have a generally long life compared even to other Europeans. Race could affect access to medical services, to renal dialysis, and to renal transplantation (depending on blood group and tissue type histocompatibility). These effects and limitations need to be more clearly stated. The choice of timing of dialysis is complex as implied. Presumably there is only one major renal unit involved serving this study so their policy is what would have determined the matter. Did this alter between 1999 and 2010? What type of dialysis treatment to give people again is a complex matter. Again, the local dialysis unit will be able too describe trends over this period of time. Certain age, race, home circumstance,

	educational and medical biases can shape dialysis choices, and, as stated, as peritoneal dialysis fails, so HD is usually the dialysis of last resort. The cardiovascular, cancer and psychological screening of potential transplant recipients will explain their reduced mortality compared to an older frailer cohort remaining on dialysis. This needs to be explained. Conservative (non-dialytic) treatment of terminal renal failure has increased very significantly over the time period here, and again, the local renal and dialysis unit will be able to mention how many CKD stage 5 patients known to them died without receiving dialysis treatments. All of the above information would be important additional context to help interpret the findings presented, which otherwise seem clear and consistent with previous studies in this field

REVIEWER	Kristine Hommel Department of Nephrology, Rigshospitalet, Copenhagen University Hospital, Denmark
REVIEW RETURNED	17-Nov-2013

GENERAL COMMENTS	Chronic kidney disease is a progressive disease with increasing mortality and end-stage kidney disease is not compatible with life without renal replacement therapy. Therefore, it does not make sense to compare mortality before and after start of this treatment. This observational study is not appropriate to decide on when to start renal replacement therapy. Only randomised clinical studies should be used to decide on when to start renal replacement therapy.

VERSION 1 – AUTHOR RESPONSE

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Reviewer Name: David Goldsmith
Guy's and St Thomas' Hospitals London UK
Neovius et al try to show, from a single population group in Stockholm Country over 11 years, the impact of chronic kidney disease on mortality.
CKD STAGE DEFINITION
I think for a general journal a brief reminded of CKD stages is appropriate.
Comment: We agree. In the methods section, we had defined the CKD stages used:
Page 5/Quality Register Sources/2nd sentence: *"Stages 4 and 5 were defined as an eGFR of 15-29 and*
<15, respectively."
We have now added text about CKD stage categorization in both the abstract and the introduction as follows:
ABSTRACT: ***"Objective:*** *To compare mortality in chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min/1.73m2), peritoneal dialysis, hemodialysis, and transplanted patients."*
INTRODUCTION: *"Mortality is substantially elevated in chronic kidney disease (CKD) and dialysis patients,1-3 with some studies describing CKD patients in stages 4 and 5 (estimated glomerular filtration rate [eGFR] 15-29 and <15 ml/min/1.73m2, respectively) as having mortality rates approaching the rates in dialysis."*
ALBUMINURIA, PROTEINURIA & ACUTE KIDNEY INJURY CASES

The lack of any data on albuminuria, proteinuria, as powerful a driver for adverse outcomes as is GFR, needs to be clearly stated at the outset. I am assuming also that all biochemical values have been repeated in all patients to assure that this population is free from acute kidney injury cases.

Comment:

We fully agree that albuminuria is a powerful predictor of cardiovascular morbidity and mortality, and that further subgrouping of the CKD population could have been interesting by levels of albuminuria. This was done in the meta-analysis by Matsushita et al, which we highlight in the introduction (2nd para, last sentence). Unfortunately, data on albuminuria were much less complete than the data on eGFR over the study period. Therefore we did not deem an analysis further stratified by albuminuria feasible.

As requested by the reviewer, we now acknowledge the lack of albuminuria data at the outset, in the methods section:

Page 5/Quality Register Sources/1st para/last sentence: "*Data on albuminuria were incomplete and therefore no analyses by albuminuria status were performed."*

In the discussion section, we have also added albuminuria as a limitation:

Page 9/Last sentence: *"The analyses were also limited by lack of albuminuria data."*

Patients with acute kidney injury are not in the register, only patients with chronic kidney disease.

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UNDERESTIMATION OF KIDNEY DISEASE PREVALENCE

The real prevalence of kidney disease will be higher than the cases reported here, for this reason (above) and also the lack of data on people with normal GFR but significant urinary protein excretion.

Comment: Yes, we fully agree. In the discussion section we had already acknowledged this underascertainment:

Page 9/Strengths & weaknesses/3rd para: *"One limitation was that while all renal replacement therapy patients in Stockholm County were included,* ***an unknown number of CKD patients were missed****: CKD is under-diagnosed and many patients are identified only at dialysis start, or die before identification. Our results should therefore only be generalized to CKD patients in nephrology care."*

In the methods section, we have further specified that the CKD stage 4 and 5 patients are only patients "*registered at Karolinska and Danderyd University Hospital from 1999 to 2010*" [page 5/Quality Register Sources]. To this we have added:

"This does not include all CKD stage 4 and 5 patients in the county, as some get care elsewhere and some remain undetected."

We also highlight this under the summary "strengths and limitations", bullet 3:

"Although all renal replacement therapy patients in the catchment area were included, an unknown number of chronic kidney disease stage 4 and 5 patients were likely missed, as the condition is underdiagnosed."

RACE / ETHNICITY

There are no data I can find on race. Certain parts of Sweden eg Malmo have very significant ethnic diversity. This is less so in Stockholm but has increased there over time. Race is a complex factor with

CKD - IndoAsian and Afro-Carribean people have a much higher incidence of renal disease than Whites. Their longevity and mortality may well be different from white Swedes, who have a generally long life compared even to other Europeans. Race could affect access to medical services, to renal dialysis, and to renal transplantation (depending on blood group and tissue type histocompatibility). These effects and limitations need to be more clearly stated.

Comment: Thank you for this comment. We agree that race/ethnicity may be important in mortality analyses, and that it is indeed a complex factor. Also, the granularity level needed for such an analysis is currently not available in Sweden. Unfortunately (from an epidemiological perspective), race/ethnicity is not kept in any national register (and we are even unsure about the legality to keep such information in registers in Sweden). The only information that is anywhere near ethnicity is country of birth grouped into broad categories, which clearly is a very crude proxy as the population of second generation immigrants is large and that different ethnicities co-exist in most countries. Therefore we cannot determine whether there is an ethnicity imbalance between the CKD patients and the population controls. This limitation we now acknowledge in the discussion section:

Discussion/page 9/last para

"For example, ethnicity may affect mortality through various mechanisms, including access to renal transplantation (depending on blood group and tissue type histocompatibility). We did not have access to ethnicity data and could therefore not determine whether there was an imbalance between cases and controls."

3

DIALYSIS TIMING

The choice of timing of dialysis is complex as implied. Presumably there is only one major renal unit involved serving this study so their policy is what would have determined the matter. Did this alter between 1999 and 2010?

Comment:

Three units were included in this study (Karolinska Solna, Karolinska Huddinge, and Danderyd), two of which belong to the Karolinska university hospital (merger of Karolinska Solna and Karolinska Huddinge in 2004). The renal clinics in Stockholm have had close collaboration throughout the study period and followed the same clinical treatment program for commencing RRT. There were no financial, or other, incentives to start early at any cite. No major shifts in policy were made during the study period, which appears to be reflected in the similar mortality rates for CKD patients analysed by calendar period (see comment below and Kaplan-Meier curve).

TYPE OF DIALYSIS

What type of dialysis treatment to give people again is a complex matter. Again, the local dialysis unit will be able to describe trends over this period of time. Certain age, race, home circumstance, educational and medical biases can shape dialysis choices, and, as stated, as peritoneal dialysis fails, so HD is usually the dialysis of last resort.

Comment: In Table 1 we describe the characteristics of PD and HD patients regarding age, sex, education level and comorbidity status. HD patients are slightly older but generally similar in terms of sex, education level and comorbidity status. Unfortunately, we do not know about home circumstances and other potential social channeling factors that may be at play. We have added the following to the discussion:

Discussion/Page 9/2nd but last para

"Prognostic factors may also be worse than in patients selected for peritoneal dialysis, although they were similar in terms of comorbidity status and education level. Other channeling variables may still influence relative mortality between the groups."

SCREENING FOR TRANSPLANTATION

The cardiovascular, cancer and psychological screening of potential transplant recipients will explain their reduced mortality compared to an older frailer cohort remaining on dialysis. This needs to be explained.

Comment: We agree. In the discussion we write the following:

Discussion/Page 9/2nd but last para

"To be selected for transplantation several prognostic factors are also considered, such as age and diabetes (which we adjusted for), but also general frailty (which we did not capture beyond certain comorbidities)."

Also, we point out the major differences in comorbidity status and age in the results section and Table 1:

*"Regarding selected register-identified comorbidities, the CKD and dialysis patients were similar, while the younger transplanted group displayed much lower prevalence. More than 30% of patients (except the transplanted group) had diabetes, compared to 3-7% in the matched general population (**eTable 2**). Approximately 80% of patients had circulatory disease history at inclusion, with about 10% having had myocardial infarction and 10% stroke (except transplanted patients)."*

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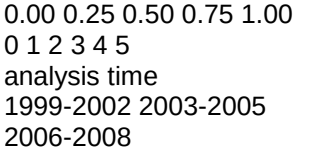
CONSERVATIVE TREATMENT OF CKD 4&5

Conservative (non-dialytic) treatment of terminal renal failure has increased very significantly over the time period here, and again, the local renal and dialysis unit will be able to mention how many CKD stage 5 patients known to them died without receiving dialysis treatments. All of the above information would be important additional context to help interpret the findings presented, which otherwise seem clear and consistent with previous studies in this field

Comment:

The number of patients dying before dialysis start are shown in Figure 1, top left panel. In terms of calendar period trends in survival in CKD, we do not present such data in the manuscript. Below we show the survival of CKD patients enrolled in three different time periods: 1999-2002 vs 2003-2005 vs 2006-2008). There are no obvious calendar period trends in mortality among these patients. If needed to provide further context, we could add this graph to the supplementary web appendix.



Kaplan-Meier survival estimates
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Reviewer Name: Kristine Hommel

Department of Nephrology, Rigshospitalet, Copenhagen University Hospital, Denmark

COMPARING MORTALITY ESRD WITH CKD STAGE 4+5 NONSENSICAL?

Chronic kidney disease is a progressive disease with increasing mortality and end-stage kidney disease is not compatible with life without renal replacement therapy. Therefore, it does not make sense to compare mortality before and after start of this treatment.

Comment: We make mortality comparisons with matched general population controls to assess the excess mortality in both CKD stage 4+5, HD, PD and transplantation in a refined way compared to previous comparisons with life-table data. We also compare mortality directly between CKD stage 4+5, transplantation, HD and PD. In the literature, it is not uncommon to discuss mortality in CKD stage 4+5 versus mortality in dialysis (see eg Go et al, N Engl J Med, 2004; ref 1), and claims have been made that mortality in CKD 4+5 is similar to dialysis mortality rates.

We do not understand the rationale given by the reviewer that the comparison is nonsensical just because end-stage renal disease is incompatible with life without dialysis. Dialysis is not rationed in Sweden, but freely available to all who need it. This is also the case in most if not all other developed countries. Therefore we do not see why mortality cannot be compared between patients with CKD 4+5 vs dialysis patients, just as CKD 4+5 can be compared with mortality in the general population.

We do acknowledge that it is not free from complications to compare mortality rates (just as it is not free from complications trying to compare mortality of different diseases or in different segments of the general population):

Discussion/Page 9/2nd para:

"Secondly, comparing mortality estimates in the respective health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the CKD health state.16

However, such channeling of survivors is likely to decrease the mortality differential between CKD and

dialysis patients."

Also, in the summary strengths and limitations we state in the 4th bullet:

"Direct comparison of mortality across different health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the chronic kidney disease health state"

DECISION ABOUT EARLY VS LATE START OF DIALYSIS

This observational study is not appropriate to decide on when to start renal replacement therapy. Only randomised clinical studies should be used to decide on when to start renal replacement therapy.

Comment: We fully agree and we also cite RCT evidence regarding early start in the discussion section, page 10, last para, where we cautiously state what our findings *indicate*:

"A recent randomized controlled trial gave no indication that early start was beneficial for survival.22 Our data showing much higher mortality in both peritoneal dialysis and hemodialysis compared to CKD patients, together with previous findings, indicate that caution should be exercised before initiating dialysis."

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DESCRIPTION OF CKD POPULATION

In methods section, the CKD population needs a better description. Are they identified in an outpatient clinic?

Comment:

We have added that they were identified in the outpatient setting at Karolinska and Danderyd University Hospital (page 5/Quality Register Sources/first para).

COMORBIDITY DEFINITION

Definition of comorbidity is lacking.

Comment:

Comorbidity is described on page 5/The National Patient Register/2nd paragraph:

"From inpatient and outpatient care registered in the National Patient Register, data on hospital visits listing diabetes, malignancies, circulatory disease, and chronic obstructive pulmonary disease were gathered. Visits listing these diagnoses were searched for during the last ten years (ICD-9 and ICD-10

*codes provided in **eTable 1**)."*

VERSION 2 – REVIEW

REVIEWER	David Goldsmith Guy's and St Thomas' Hospitals London
REVIEW RETURNED	16-Jan-2014

GENERAL COMMENTS	I believe it is now fit for publication